Human Milk Fortifiers and Their Role in Neonatal Nutrition

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Introduction

Breast milk is becoming widely recognized as the superior form of nutrition for infant feeding. When compared to formula, infants fed breast milk are less likely to have gastrointestinal complications, higher IQ, and positive long term effects such as reducing their rates of obesity and diabetes as adults (Chantry et al. 2015). However, breast milk was never made to replace a placenta and for premature infants, they will need a more complex diet to ensure their adequate growth and development. In this regard, human milk fortifiers have revolutionized neonatal nutrition. However, there is still debate on the clinical outcomes in amplifying the nutrients in breast milk when combined with human-based milk fortifier (HBF), or bovine-based milk fortifier (BBF), and whether or not an exclusively human milk diet has positive effects on infant health.

Components of Breastmilk

In order to fully understand the differences between HBF and BBF a brief look into the unique qualities in breast milk is necessary. Breast milk is primarily composed of lipids, ranging from 40-55% of the total energy (Andreas et al. 2015). Triacylglycerides comprise 98% of the lipid profile in breast milk, followed by diacylgylcerides, monoacylglycerides, free fatty acids, phospholipids, and cholesterol, all of which are packaged into milk lipid globules (Andreas et al. 2015). Sphingomyelins are present in the membrane of this globule and are critical for central nervous system myelination, in addition to improving the neurobehavioural development of low-birthweight infants (Andreas, Kampmann, & Mehring Le-Doare, 2015). The lipids in breastmilk have also been associated with potent cytolytic effects on intestinal parasites,

gram-positive bacteria, and yeast (Andreas et al. 2015). Lysozymes, which are present in human milk 3,000 times more than in bovine milk, can break down the outer cell wall of gram-positive bacteria and in some gram-negative bacteria. The immunoglobulins in lactation are widely known to provide protection to the infant while their immune system matures. Secretory IgA (SIgA) is the primary antibody present in breast milk, protecting against pathogens via a multitude of ways. SIgA prevents adherence to epithelial cell surfaces by immobilizing pathogens and neutralizes toxins and virulence factors. Due to SIgA's relative aversion to proteolysis, it can withstand the gastrointestinal tract's quick cell turnover rate and further protect against pathogens (Andreas et al. 2015). Breast milk's SIgA can protect from a variety of pathogens, such as: *Vibrio cholerae, Campylobacter, Shigella, Giardia lamblia,* and respiratory tract infections (Andreas et al. 2015). Additionally, sodium nitrate in breast milk provides better blood flow to the gastrointestinal tract which can lower rates of necrotizing enterocolitis.

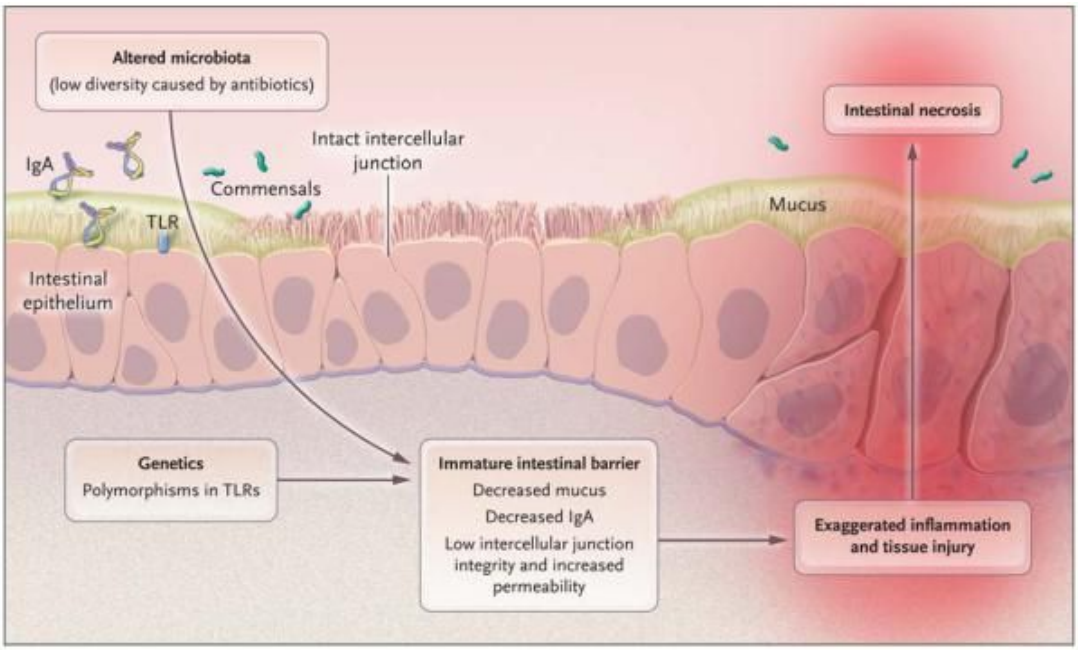
Unique Care for Preterm Infants

As neonatal intensive care modernized with improved medical interventions, infants' survival rates also improved. The primary concern for premature infants is immaturity of the respiratory system, resulting in low surfactant in the lungs to maintain breathing. However, with the introduction of Continuous Positive Airway Pressure (CPAP) in 1971, infants who received this intervention had an 80% survival rate (Dillard 2016).

Similarly, feeding was a concern for infants in the 1970's because of the reliance on term formula. Formula contained 82% casein protein and 18% whey protein. It became increasingly apparent that this ratio increased acid accumulation in the gut, or could even cause a lactobezoar.

A lactobezoar is a solid mass of protein that would collect and potentially perforate the stomach, threatening the life of an infant. As the ratio became closer to that of breast milk (40% casein, 60% whey) feeding resilience began to increase both in initiation and volume tolerance (Dillard 2016).

One of the most fearsome diseases that can affect a premature infant is necrotizing enterocolitis (NEC) which is associated with bacterial infections, poor perfusion of blood in the intestines, and enteral feeding. The peak incidence (15%) of NEC and the leading cause of death in this developmental stage, is around 24 weeks gestation, a gestational age where being categorized as very low birth weight (<1500 grams) is more common. Those who survive are at a higher risk for significant neurodevelopmental impairments as well as a host of other short and long term complications (Learning in 10 2018). Although it is not known why this disease occurs in premature infants, nor is there a cure, human milk has been shown to be protective against NEC (Chantry et al. 2015).



(Neu and Walker 2011)

Human Milk Fortifiers (HMF)

Although breast milk's benefits are expansive, it cannot compare to the rapid development that occurs in utero during the third trimester. Therefore, as neonatal care became more impressive, so did the need for a nutritional product that could boost the advantageous profile of breast milk. A mother's milk will have a higher protein content if their child is born prematurely for about one month, a necessary change to promote growth, yet one that is only short term. However, the use of non-sterile powder formulas is generally discouraged in this immunocompromised population due to the fear of infection. Fortifiers became a means to extend this higher protein content to aid in the rapid growth of the premature infant. The American Academy of Pediatrics (AAP) recommends fortifying mother's milk or pasteurized donor human milk with protein, minerals, and vitamins to ensure optimal nutrition intake. (Bakewell-Sachs et al. 2009).

Breast milk and its many benefits, briefly spoken about above, demonstrates that it is the optimal food source for an infant of any age. Coupled with the knowledge of the unique physical condition a premature infant experiences, the need to add fortifier to breast milk is apparent. Currently, the only human-based human milk fortifier regulated by the FDA and on the market is by Prolacta Bioscience.

Ingredients

In the neonatal world, daily energy requirements are calculated and divided by kilograms as a reference point. For premature infants being enterally fed, the requirements are between 105 to 130 kcal/kg per day (Texas Children's Hospital). Infants being parenterally fed need less

energy due to the concentrated dose of nutrition they receive. Additionally, being more critically ill results in less fecal energy loss, fewer episodes of cold stress, and less activity overall. Their requirements are around 90-100 kcal/kg per day (Texas Children's Hospital). Infants that are ill with a chronic illness may need more calories per day due to an increased resting energy expenditure (REE).

Nutrient Requirements of Preterm Infants in Comparison to Intakes Provided from Unfortified and Fortified Human Milk					
Nutrients	Nutrient Requirements for preterm infants <1500 g	Unfortified 20 kcal/oz Breast milk*	24 kcal/oz Breast milk + HMF*	27 kcal/oz Breast milk + HMF	30 kcal/oz high protein breast milk + HMF
Fluids ml/kg	—	180	150	133	120
Energy (kcal/kg)	120	120	120	120	120
Protein (g/kg)	4	1.8	3	3.4	4.1

*Feeding Type (content based on use of Powdered Similac HMF)

When analyzing the ingredients present in breast milk that can benefit premature babies, human milk oligosaccharides (HMOs) first come to mind. HMOs were discovered as a prebiotic that serves as a metabolic substrate for the bacteria *Bifidobacterium* which helps shape intestinal microbiota composition (Bode 2012).With over 200 identified HMOs, human milk has more complex variations and a higher concentration of HMOs than any other mammalian milk (Bode

2012). There are 5 monosaccharides that can create HMOs: glucose, galactose, N-acetylglucosamine, fucose, and sialic acid. The first two monosaccharides bond together to form the disaccharide lactose, the structural backbone of HMOs (Bode 2012). As these complex sugars are ingested, they pass through the entire gastrointestinal tract to land in the large intestine. There, among the highly dense bacterial environment, they are eaten by the bacteria and contribute to the immune system. The variety of HMO's present also diversifies the different biological functions that they contribute to. HMO's functions include:

- Enhance and sustain growth of beneficial gut bacteria (Smilowitz et al. 2014).
- Prophylactically bind harmful bacteria, viruses, and toxins to allow for their excretion (Smilowitz et al. 2014).
- Improve intestinal epithelial barrier function by supporting beneficial bacteria (Smilowitz et al. 2014).
- Support maturation and regulation of the immune system (Jantscher-Krenn and Bode 2012).

Prolacta fortifier claims to be the only nutritional product that contains a wide variety of HMOs due to their large starting pools. Additionally, traditional pasteurization methods do not affect the variety of the HMOs in their fortifying products.

Indicated Use

There is not a clearly defined initiation process of beginning to fortify milk with human milk fortifier, and therefore each hospital's protocol may differ slightly. Forsyth Medical Center in Winston Salem, North Carolina begins fortifying with human milk fortifier for infants with a

birth weight <2000 grams, gestational age < 34 weeks, or any premature infants demonstrating inadequate intake or growth. HMF is initiated when an infant is tolerating feeds of 80 mL/kg/day at a dose of 1 pack per 50 mL. Once tolerating 100 mL/kg/day, the dose is increased to 1 pack per 25 mL. Similarly, the University of Iowa Stead Family Hospital begins fortifying milk for all breast milk fed infants weighing less than 2000 grams. Infants weighing 2000 – 2500 grams may also benefit from the addition of HMF, particularly if they are SGA or demonstrated poor intake and/or growth (Guidelines for the use of human milk ...). Initiation protocol is as follows:

1. Human Milk Fortifier (24 kcal/oz) should be initiated when the infant is tolerating breast milk feeds of > 25 ml\L/day. Infants receiving 25 mL of breast milk on the first day of feeds should wait until day of life three or four before starting HMF.
2. Infants who have been tolerating breast milk and HMF feeds and are made nil per os (NPO) should be restarted on breast milk and HMF feeds.
3. Indications for using concentrated breast milk feeds (27 kcal/oz or 30 kcal/oz high protein) in infants include:
    a. Fluid restriction < 140 ml/kg
    b. Poor weight gain (< 10 – 15 g/kg/d) on 120 kcal/kg of 24 kcal/oz Breast Milk and HMF
    c. Metabolic bone disease (alkaline phosphatase > 600 U/L) with poor bone mineralization on x-ray requiring increased intakes of calcium and phosphorus. (Guidelines for the use of human milk ...)

Monitoring guidelines include checking electrolytes on a weekly basis until they are within a normal range and the infant is no longer receiving intravenous fluids or oral electrolyte supplements, as well as paying close attention to calcium and phosphorous levels due to the possibility of high mineral intake from fortification.

The Academy of Breastfeeding Medicine suggests that the discharge plan for infants receiving fortified milk begin one week in advance, transitioning the infant to unfortified human milk, ad libitum. During this time their growth will be monitored, and if not exclusively breastfeeding, monitoring milk intake as well. If growth is adequate, this is an appropriate discharge plan. However, if discharge follow-up can be scheduled quickly (within one or two days), the infant can transition off fortified human milk, ad libitum at any time before discharge without one week of inpatient monitoring (Chantry et al. 2015).

Effectiveness

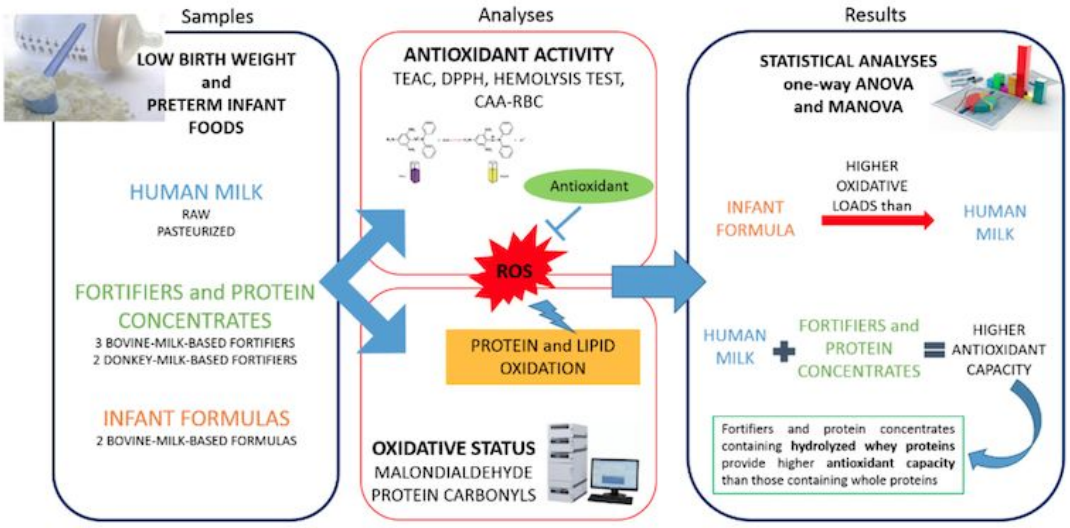
There is a small, but growing, body of literature on the efficacy of HBF and how it's implementation could impact neonatal nutrition. Furthermore, with the new onset of human based human milk fortifier (HBF), there is an increasing amount of research dedicated to it's comparison to bovine based human milk fortifier (BBF).

In a study comparing the in vitro antioxidant and oxidative compounds within raw and pasteurized human milk, two different preterm infant formulas, three bovine milk-based fortifiers and two experimental donkey milk-based fortifiers, HBF was shown to reduce rates of NEC (Pozzo et al. 2019). Incidence of NEC was lower (Assad et al. 2016) in very low birth weight infants on an exclusively HBF when assessed in a level III NICU. However, in very preterm

infants there has not been conclusively statistically significant differences in NEC incidence nevertheless, significantly fewer infants fed the complete exclusive human milk diet (EHMD) experienced surgical NEC (Cristofalo et al. 2013) which has a higher mortality rate.

The primary outcome of the latter study was the number of days on parenteral nutrition each preterm infant experienced. The median amount of days was 36 versus 27 in BBF and HBF fed infants, respectively (Cristofalo et al. 2013). Additionally, in the same study as above that compared the in vitro antioxidant and oxidative compounds within raw and pasteurized human milk, HBF was shown to decrease duration of parenteral nutrition (Pozzo et al. 2019).

Some theories predict that the positive results we see are not due to the antioxidative components within human milk, but rather the results are from minimizing the oxidative components found in other non-human-based milks. Furthermore, in a study measuring fecal calprotein, a marker of gut inflammation and a risk factor for NEC, in infants born weighing less than 1250 grams and fed an exclusive human milk diet, the use of HBF in comparison to BBF did not show an improvement in feeding tolerance, reduced mortality, nor morbidity. (O'Connor et al. 2018). One study included 293 infants between gestational ages 23 to 34 weeks and birth weights between 490 and 1700 grams. Feeding intolerance occurred less often, number of days to full feeds was lower, incidence of NEC was lower (Assad et al. 2016) and total hospitalization costs were lower by up to $106,968 per infant in those fed an EHM diet compared with the other groups.



(Pozzo et al. 2019)

Average weight gain per day was similar among the four groups (18.5 to 20.6 grams per day) (Assad et al. 2016). However, when compared specifically to bovine-based human milk fortifier, there is not a consensus on whether either one is superior than the other as far as weight gain. In regards to a study conducted on extremely low birth weight infants (<1000 grams), there was no conclusion that HBF was better than BBF. In fact, those receiving HBF had a significantly lower growth velocity than those receiving BBF (Eibensteiner et al. 2019). An EHMD has been shown to decrease another comorbidity of prematurity, severe retinopathy. When compared to BBF, HBF reduced incidence of retinopathy, even though infants were receiving human milk in both study groups (Taylor 2019). Additionally, morbidities such as late-onset sepsis and bronchopulmonary dysplasia are decreased with higher doses of human milk, though significant differences are not apparent in exclusive human milk diet studies (Taylor 2019) which shows the potential promise in conducting further research on EHMD's.

The field of EHMD is relatively new, and therefore there is yet to be consensus on the true impact.

Cost

The immunoprotective factors in human milk may also play a role in reducing medical costs incurred by both parents and hospitals. It is unclear if the effects are seen due to breast milk lining the immature gut mucosa or rather because of the absence of harmful antigens that can be found in non-human-based products. In 2011, the adjusted incremental costs of medical and surgical NEC above the average cost incurred for extremely premature infants in the NICU was $74,004 and $198,040 per infant, respectively.

"Extremely premature infants fed with 100% human-milk based products had lower expected NICU length of stay and total expected costs of hospitalization, resulting in net direct savings of 3.9 NICU days and $8,167.17 (Ganapathy et al. 2012)" Additionally, in a retrospective study conducted on 293 infants, total hospitalization costs were lower by up to $106,968 per infant in those fed an exclusively human milk diet compared with the other groups. Similarly, a study including 293 infants between gestational ages 23 to 34 weeks and birth weights between 490 and 1700 grams showed that feeding intolerance occurred less often, number of days to full feeds was lower, incidence of NEC was lower, and total hospitalization costs were lower by up to $106,968 per infant in those fed an EHM diet compared with the other groups (Assad et al. 2016).

Discussion

Human milk based fortifier has been shown to reduce the incidence of NEC in very low birth weight infants, however this finding was not found in preterm infants. The latter study also showed reduced surgical NEC when exposed to an exclusive human milk diet in those same preterm infants. Additionally, there has been research to show that HBF decreased the amount of days on parenteral nutrition, feeding intolerance, number of days to full feeds, and costs per infants were lowered by over $100,000. However, when looking specifically at gut inflammation, there did not seem to be a difference between HBF and BBF. Human milk has been cited as a lower inflammatory food and inflammation is known to contribute to NEC, however more studies need to be conducted on how these two factors interplay within an infants gut and what other factors within the NICU setting may be contributing to inflammation. Furthermore, growth velocity does not appear better in infants fed with HBF versus BBF, however according to the WHO growth charts, healthy term, breastfed babies tend to have a lower weight at around three months compared to formula fed babies which may be human's biological inclination reflected in NICU care. Additionally, HBF has been shown to decrease other comorbidities in the preterm infants including, severe retinopathy, late-onset sepsis, and bronchopulmonary dysplasia. As this budding area of research expands, the ultimate motive is to create a protocol surrounding human milk fortification in NICU settings that is backed by evidence-based research.

Most of the aforementioned studies did not look at the discrepancies between their results and races of the infant and mother. As is well-documented, there are significant health disparities in America, which are similarly reflected in the NICU setting. As initiative is being taken in the

public health world to increase access and ease of breastfeeding to people of color and their infants, the role of human milk fortifier is yet to be addressed. As research expands on the benefits of an EHMD, there is the potential for advocating for this type of diet and how it may help reduce racial inequities within the neonatal realm.

Public Health and Clinical Implications

As with all healthcare in the United States, there are significant inequalities due to structural racism that need to be accounted for if access to optimal care for all infants is to be a goal. According to the CDC, compared to 86.6% of non-Hispanic white infants and 82.9% of Hispanic white infants only 74% of non-Hispanic black infants were ever breastfed (CDC 2019). The world of motherhood is convoluted with twists and turns of guilt, judgement, and unwavering cultural norms. Coupled with a new birth of a sick child, many factors can influence a woman's decision to start and continue breastfeeding. Having a lack of support both in the familial or cultural sense, limited information about breastfeeding, and an unsupportive work environment can all contribute to a women's early cessation of breastfeeding (Anstey et al. 2017). Additionally, some of these factors disproportionately impact women of color, especially black women who are twice as likely to give birth to premature babies (14%) in comparison to white mothers (9)% (Preterm Birth | Maternal and Infant H...). Black women are more likely to be affected by an earlier return to work, inadequate education about breastfeeding from providers, and lack of access to breastfeeding support that all can impact her decision to breastfeed and the duration of breastfeeding (Johnson et al. 2015). One study examining hospital-based support for breastfeeding found that facilities less likely to meet five indicators

for supportive breastfeeding practices were also facilities within zip codes that had higher than the national average of black residents. These practices included early initiation of breastfeeding, minimal use of breastfeeding supplements and pacifiers, rooming-in, and providing support post-discharge for mothers (Lind et al. 2014). The hurdles that black women have to face will undoubtedly affect their relationship with breastfeeding, regardless if it is the most beneficial nutrition for their babies. The socioecological model (SEM) demonstrates how the environment that one lives in can affect their most intimate decision making. The information surrounding the benefits of breastfeeding is rather ubiquitous, so rather than a focus on *why* breastfeeding is best, public health efforts should be placed on educating providers and policy makers on *what* is making sustaining breastfeeding so hard, especially for mothers of sick babies. In 2011, *The Surgeon General's Call to Action to Support Breastfeeding* outlined 20 action steps to support breastfeeding across various sectors of society, including a call to better understand and address breastfeeding disparities (Lowe 2011). "A U.S.-based review of randomized trials evaluating breastfeeding interventions targeting minorities showed that group prenatal education, peer counseling interventions, breastfeeding-specific clinic appointments, and enhanced hospital practices/WIC-based services positively affected breastfeeding outcomes among minority women." Moreover, the CDC is currently funding a quality improvement project in hospitals to support the implementation of these evidence-based maternity care practices (Anstey et al. 2017).

Furthermore, there are socioeconomic factors to consider. Infants eligible and who participate in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) are the least likely to ever be breastfed (75.5%), in comparison to those that are eligible

but do not participate in WIC (89%) and infants who are not eligible (92.7%) (CDC 2019). As the importance of human milk becomes a standard in medical practice, the question has to be framed in such a way that those who are marginalized are not further disenfranchised in the pursuit of optimal medicine. In the clinical setting, these health disparities can manifest themselves in mothers not having the resources, nor the support to sustain breastfeeding for their infants in the NICU. These infants may be more likely to experience a myriad of health outcomes that can affect both short and long term development, further perpetuating the cycle of poor health in families that struggle to break free.

Conclusion

Human milk has extraordinary qualities that are uniquely designed for infants and their nutritional needs, including those related to immunity, neurodevelopment, and gut health, all of which are further magnified when considering the care of preterm infants. In order to achieve adequate growth these immunocompromised infants need breastmilk to be fortified. As of now, there is no conclusive evidence that human milk based fortifiers are superior to bovine milk based fortifiers, however, their effects of shortening duration of parenteral nutrition, and reducing rates of NEC and costs have been documented. Although there is no question that breast milk is the optimal form of nutrition for an infant, there are racial and socioeconomic disparities across all breastfeeding targets, inclusive of initiation, exclusivity, and duration. As more studies are conducted on this newer supplement in the world of neonatal nutrition, there needs to be a thoughtful discussion on how best to ensure all sick babies are provided human milk, whether fortified or not.

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